The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000152.5(GAA):c.2383G>T (p.Glu795Ter)

Version: 2.0

CA401325061

649354 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9f7236b9-e0fe-4a9f-938a-7b069c5034c4
Approved on: 2023/6/27
Published on: 2023/9/5

HGVS expressions

NM_000152.5:c.2383G>T
NM_000152.5(GAA):c.2383G>T (p.Glu795Ter)
NC_000017.11:g.80117651G>T
CM000679.2:g.80117651G>T
NC_000017.10:g.78091450G>T
CM000679.1:g.78091450G>T
NC_000017.9:g.75706045G>T
NG_009822.1:g.21096G>T
ENST00000570803.6:c.2383G>T
ENST00000572080.2:c.*521G>T
ENST00000577106.6:c.2383G>T
ENST00000302262.8:c.2383G>T
ENST00000302262.7:c.2383G>T
ENST00000390015.7:c.2383G>T
ENST00000573556.1:n.336G>T
NM_000152.3:c.2383G>T
NM_001079803.1:c.2383G>T
NM_001079804.1:c.2383G>T
NM_000152.4:c.2383G>T
NM_001079803.2:c.2383G>T
NM_001079804.2:c.2383G>T
NM_001079803.3:c.2383G>T
NM_001079804.3:c.2383G>T

Pathogenic

Met criteria codes 4

PM2_Supporting PVS1 PP4_Moderate PM3_Supporting

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.2383G>T (p.Glu795Ter) variant in GAA is a nonsense variant that is predicted to cause a premature stop codon in biologically-relevant-exon 17/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Two patients have been identified with GAA activity in the deficient range; one of these patients has no detectectable GAA protein on Western blot of protein from skin fibroblasts i.e. CRIM-negative (clinical diagnostic laboratory) (PP4_Moderate). The CRIM-negative patient is compound heterozygous for the variant and a variant that has been classified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (LD VCEP) as pathogenic, c.2560C>T(p.Arg854Ter). The phase is unknown (clinical diagnostic laboratory). The other patient is compound heterozygous for the variant and c.1904A>C (p.Asp635Thr). The allelic data from this patient will be used in the classification of p.Asp635Thr and is not included here to avoid circular logic (PM3_Supporting). The variant is absent in gnomAD v2.1.1. (PM2_Supporting).There is a ClinVar entry for this variant (Variation ID: 649354). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LD VCEP (Specification Version 2.0): PVS1, PP4_Moderate, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP, June 27, 2023).

Met criteria codes

PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1.
PVS1	✔	The NM_000152.5:c.2383G>T (p.Glu795Ter) variant in GAA is a nonsense variant that is predicted to cause a premature stop codon in biologically-relevant-exon 17/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4_Moderate	✔	Two patients have been identified with GAA activity in the deficient range; one of these patients has no detectectable GAA protein on Western blot of skin fibroblasts i.e. CRIM-negative (clinical diagnostic laboratory) (PP4_Moderate).
PM3_Supporting	✔	One patient is compound heterozygous for the variant and a variant that has been classified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (LD VCEP) as pathogenic, c.2560C>T(p.Arg854Ter). The phase is unknown (clinical diagnostic laboratory). Another patient is compound heterozygous for the variant and c.1904A>C (p.Asp635Thr). The allelic data from this patient will be used in the classification of p.Asp635Thr and is not included here to avoid circular logic. Total 0.5 points (PM3_Supporting).

Curation History

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